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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,241	01/17/2002	Bernhard Hauer	50531	6324

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,241	HAUER ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-10,13-15 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on June 26, 2006, amending claims 11-12 and 16, has been entered.

Claims 1-22 are pending. Claims 1-10, 13-15 and 19-22 are withdrawn. Claims 11-12 and 16-18 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on June 26, 2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32-33 and 35-37 and claims 34 and 38-41 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "the ω-hydroxylatable fatty acid derivative" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-12 and 16-18 are drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids from fatty acids recited in claim 11 by using a cytochrome P450 monooxygenase and electron donor system comprising a non-electrode-bound source of electrons and a mediator. These claims are drawn to a method of enzymatic production of terminally or subterminally hydroxylated fatty acids using any or all cytochrome P450 monooxygenase, including any recombinants, variants and mutants from any source and/or any or all electron donor system comprising a non-electrode-bound source of electrons. Therefore, the claims are drawn to a method for enzymatic production of terminally or subterminally hydroxylated fatty acids using a genus of cytochrome P450 monooxygenase and/or any or all electron donor system comprising a non-electrode-bound source of electrons. There is insufficient descriptive support for the genus comprising any or all cytochrome P450 monooxygenases and genus comprising any or all electron donor system comprising a non-electrode-bound source of electrons. The specification only teaches a method of

hydroxylating fatty acids described in Examples 2-4 of the specification using specific cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate electron donor system. These examples are not enough and does not constitute a representative number of all the species to describe a method of hydroxylating the recited fatty acids using a genus of cytochrome P450 monooxygenase, including any or all mutants, variants and recombinants, and any or all electron donor system comprising a non-electrode-bound source of electrons. There is also no evidence on the record of the relationship between the structure of a *Bacillus megaterium* cytochrome P450 monooxygenase and the structure of a polynucleotide encoding any or all any recombinants, variants and mutants of any cytochrome P450 monooxygenase nor the relationship between the structure of a zinc/Co(III)sepulchrate electron donor system and the structure of any or all electron donor system comprising any or all non-electrode-bound source of electrons. Therefore, the specification fails to describe a representative species of a genus of cytochrome P450 monooxygenase and genus of any or all electron donor system comprising any or all non-electrode-bound source of electrons used in a method of hydroxylating fatty acids.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 11-12 and 16-18.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov <http://www.uspto.gov>.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Examiner's use of the standard USPTO biotechnology rejection is misplaced because the instant invention is drawn to a novel method for the enzymatic production of terminally or subterminally hydroxylated fatty acids, not an isolated gene and/or gene product. Examiner respectfully disagrees. While it is true that the instant invention is drawn to a method claim, the claims still involve a genus comprising any or all cytochrome P450 monooxygenase. In *University of Calfornia v. Eli Lilly & Co.*, 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, the claims are drawn to a method involving a wide genus comprising any or all cytochrome P450 monooxygenase, isolated from any or all source, including any or all mutants, recombinants or variants thereof, and a wide genus comprising any or all electron donor system comprising any or all non-electrode-bound source of electrons.

Further, the recitation of "cytochrome P450 monooxygenase (E.C. 1.14)" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "cytochrome P450 monooxygenase (E.C. 1.14)" proteins, the functional definition of the

genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Applicants argue that a single species may be enough to identify the entire genus. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe the whole genus of any or all electron donor system comprising any or all non-electrode-bound source of electrons and the whole genus of any or all variants, recombinant and mutants of any or all cytochrome P450 monooxygenase isolated from any or all source, including any or all variants, recombinants and mutants thereof. Further, there is no evidence on the record of the relationship between the structure of a *Bacillus megaterium* cytochrome P450 monooxygenase and the structure of any or all recombinant, variant and mutant of any or all cytochrome P450 monooxygenase, nor a relationship between the structure of a zinc/Co(III)sepulchrate electron donor system and the structure of any or all electron donor system comprising any or all non-electrode-bound source of electrons. Therefore, the specification fails to describe a representative species of the genus comprising any or all cytochrome P450 monooxygenase, including any or all variants, recombinants and mutants thereof.

Applicants also argue that cytochrome P450 monooxygenase is one of the most widely studied enzymes and combined with the teachings, suggestions and disclosure of the instant invention with the knowledge of one of ordinary skill in the art would provide all the requirements for the written description. Examiner respectfully disagrees. While the structure of some cytochrome P450 monooxygenase may be known, the instant claims are drawn to a method of using a wide genus comprising any or all cytochrome P450 monooxygenase, including any or all variants, mutants or recombinants thereof. As discussed above, the instant case the claimed genera of Claims 1 and 6 includes species which are widely variant in structure. As such, the disclosure solely functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus.

Hence the rejection is maintained.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of hydroxylating fatty acids described in Examples 2-4 of the specification using a cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate, does not reasonably provide enablement for such a method of hydroxylating fatty acids using any or all variants, mutants and recombinants of any or all cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 11-12 and 16-18 are drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids from the fatty acids recited in claim 11 using cytochrome P450 monooxygenase and electron donor system comprising a non-electrode-bound source of electrons and a mediator. These claims are drawn to a method of enzymatic production of terminally or subterminally hydroxylated fatty acids using any or all cytochrome P450 monooxygenase, including any recombinants, variants and mutants from any source, and any or all electron donor system comprising any or all non-electrode-bound source of electrons. Therefore, the claims are drawn to a method of hydroxylating fatty acids using any or all recombinants, variants and mutants of any cytochrome P450 monooxygenase having any structure and any or all electron donor system comprising any or all non-electrode-bound source of electrons having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number variants, mutants and recombinants of any cytochrome P450 monooxygenase broadly encompassed in the method of the claims. Regarding cytochrome P450 monooxygenase, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to a method of hydroxylating fatty acids described in Examples 2-4 of the specification using a cytochrome P450 monooxygenase obtained from *Bacillus megaterium* and zinc/Co(III)sepulchrate, but provides no guidance with regard to hydroxylating fatty acids using any or all cytochrome P450 monooxygenase, including variants, mutant and recombinants, and any or all electron donor system comprising any or all non-electrode-bound source of electrons. It would require undue experimentation of the skilled artisan to make hydroxylated fatty acids as claimed. In view of the great breadth of the claim, amount of experimentation required to identify and make the necessary cytochrome monooxygenase, amount of experimentation required to hydroxylate fatty acids using any or all cytochrome P450 monooxygenases and any or all electron donor system comprising any or all non-electrode-bound source of electrons, the lack of guidance,

working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the monooxygenase and electron donor system to hydroxylate any or all fatty acids as encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques and other related techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications in a polypeptide as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of hydroxylating fatty acids using any or all cytochrome P450 monooxygenase from any source and any or all electron donor system comprising any or all non-electrode-bound source of electrons because the specification does not establish: (A) a universal method to terminally and subterminally hydroxylate fatty acids using any or all cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons; (B) regions of a cytochrome P450 monooxygenase structure which may be modified without affecting

specific monooxygenase activity; (C) the general tolerance of cytochrome P450 monooxygenase to modification and extent of such tolerance; (D) a rational and predictable scheme for selecting any fatty acids , cytochrome P450 monooxygenase and electron donor system with an expectation of terminally or subterminally hydroxylating any fatty acids; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method of using any variant, mutant or recombinant of any cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons to hydroxylate said fatty acid. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of cytochrome P450 monooxygenase having the desired biological characteristics and electron donor system having the desired characterisitics, i.e. hydroxylate fatty acids, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Examiner has erroneously mandated a quantifiable number of examples from the applicants, but applicants are not required to pride even a single working example. Examiner respectfully disagrees. The Examiner did not mandate a quantifiable number of examples. Examiner has found that the specification fails to teach one of ordinary skill how to use the full scope of the monooxygenase and electron donor system to hydroxylate any or all fatty acids as encompassed by the claims, requiring an undue experimentation of the skilled artisan to make hydroxylated fatty acids as claimed. As discussed above, in view of the great breadth of the claim, amount of experimentation required to identify and make the necessary cytochrome monooxygenase, amount of experimentation required to hydroxylate fatty acids using any or all cytochrome P450 monooxygenases and any or all electron donor system comprising any or all non-electrode-bound source of electrons, the lack of guidance, working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation.

Applicants also argue that "cytochrome P450 monooxygenase" is well understood in the art and one of ordinary skill in the art would consider any cytochrome P450 monooxygenase to be enabled in the instant invention. Examiner respectfully disagrees. Even though the structure of some cytochrome P450 monooxygenases are known, as applicants have stated, the invention encompasses using any cytochrome P450 monooxygenase, including any or all mutants, variants and recombinants of any PQQGDH, and any or all non-electrode-bound source of electrons to hydroxylate said

fatty acid. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. Further, the specification does not provide a universal method to terminally and subterminally hydroxylate fatty acids using any or all cytochrome P450 monooxygenase and any or all electron donor system comprising any or all non-electrode-bound source of electrons and a rational and predictable scheme for selecting any fatty acids, cytochrome P450 monooxygenase and electron donor system with an expectation of terminally or subterminally hydroxylating any fatty acids. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of cytochrome P450 monooxygenases and electron donor system comprising any or all non-electrode-bound source of electrons that results from such experimentation.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-12 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Estabrook et al. in view of Creaser et al.

Claim 11-12 and 16-18 drawn to a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electro donor system, a cytochrome P450 monooxygenase, and oxygen, wherein said electron donor system is zinc/Co(III)sepulchrate.

Estabrook et al. (*Methods in Enzymology* – form PTO-1449) discloses a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system, a cytochrome P450 monooxygenase, oxygen, chloride ions and a hydrogen peroxide-cleaving enzyme, wherein said fatty acid is a C-12 fatty acid and wherein said electron donor system comprises an inorganic, non-electrode-bound source of electrons and a mediator (pages 45-46). The method of Estabrook et al. uses a Co(III)sepulchrate mediator of Creaser et al. because "it retains chirality during reversible oxidation-reduction" (page 45, 1st paragraph).

The difference between the reference of Estabrook et al. and the instant invention is that the reference of Estabrook et al. does not teach a method of producing terminally or subterminally hydroxylated fatty acids using a Zn metal in powder from.

Creaser et al. (J. Am. Chem. Soc – form 1449) discloses a Zn/Co(III)sepulchrate electron donor system, which pioneered for the use of Co(III)sepulchrate as mediators in electrochemical reactions (Faulkner et al., Reipa et al. – US Patent 6,126,795 and

Roberts et al. – US Patent 6,492,132), wherein the Co(III)sepulchrate mediator is the same mediator used by Estabrook et al. Creaser et al. teaches that Zn dust causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181).

Therefore, in combining the teachings of Estabrook et al. and Creaser et al., it would have been obvious to one having ordinary skill in the art to use either Zn dust as originally taught by Creaser et al. or Pt as taught by Estabrook et al. in hydroxylating fatty acids using a metal/Co(III)sepulchrate electron donor system. One of ordinary skill in the art would have been motivated to use Zn dust because Creaser et al. teaches that Zn dust causes immediate reduction and because Zn dust is widely available (Sigma). One of ordinary skill in the art would have had a reasonable expectation of success since Estabrook et al. teaches a method of hydroxylating fatty acids with cytochrome P450 monooxygenases by replacing NADPH with an electrochemically generated reduction by the mediator Co(III)sepulchrate and Creaser et al. teaches a method of generating two electrons using the mediator Co(III)sepulchrate and Zn dust as the source of electrons.

Therefore, the above references render claim 16 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that one of ordinary skill in the art would not have been motivated to combined Estabrook et al. and Creaser et al. because 1) Estabrook et al. fails to mention the work of Creaser even though the electron donor system of Creaser

et al. has been known for 20 years, 2) one of ordinary skill in the art would have expected success with a reducing agent which is soluble in the reaction mixture rather than the metal-based system of Creaser et al., as taught by Fang et al. and 3) Creaser et al. according to Sargeson et al. was regarded as a suitable redox system for inorganic and organic synthesis rather than biosynthesis. Examiner respectfully disagrees. 1) Contrary to applicant's argument, Estabrook et al. does mention the work of Creaser et al., see page 45, 4th citation. Estabrook et al.'s electron donor system is based on the work of Creaser et al. The only difference between the electron donor system used by Estabrook et al. and Creaser et al. is that Estabrook et al. uses Pt instead of Zn dust. 2) The instant rejection is not based on the combined teachings of Fang et al. or Faulkner et al, but on the combined teachings of Estabrook et al. and Creaser et al. Fang et al. does not disclose a method of hydroxylating fatty acids using an electron donor system comprising a metal, but a soluble inorganic compound, and offers one system for utilizing P450 enzymes using non NADPH reducing agents. One having ordinary skill in the art would not have looked to Fang et al. to improve/modify the method of Estabrook et al. Rather, one having ordinary skill in the art would have looked to Creaser et al. in modifying the method of Creaser et al. because Creaser et al. teaches that Zn dust causes reduction of the Co(III)sepulchrate mediator within seconds (page 3181). Therefore, it would have been obvious to one having ordinary skill in the art to use either Zn dust as originally taught by Creaser et al. or Pt in the method taught by Estabrook et al. 3)The reference of Creaser et al. is relied on its teaching of using Zn dust as the source of electrons. Estabrook et al. provides disclosure of using an

electron donor system comprising a Co(III)sepulchrate as the mediator in biosynthesis, enzyme-catalyzed hydroxylation reactions of fatty acids. In combining the teachings of Estabrook et al. and Creaser et al., it would have been obvious to one having ordinary skill in the art to use either Zn dust as originally taught by Creaser et al. or Pt in the method taught by Estabrook et al. One of ordinary skill in the art would have been motivated to use Zn dust because Creaser et al. teaches that Zn dust causes immediate reduction and because Zn dust is widely available (Sigma).

Applicants also argue use of improper hindsight reasoning and that Examiner has attempted to piece together the claimed invention using the instant claims as a guide picking and choosing elements to fit an obviousness rejection. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it should be noted that the knowledge of a Zn/Co(III)sepulchrate electron donor system was well known and within the level of one having ordinary skill in the art at the time the invention was made. With such information already available in the prior art, one having ordinary skill in the art would have been motivated to use Zn dust as a source of electrons.

Applicants also argue that the electron donor system of the instant invention using Zn dust yields reaction rates twice as great when compared to the electron donor system of Estabrook et al. The instant rejection is not based on Estabrook et al. alone. The relative rates of the electron donor system for Estabrook et al. and Zn/Co(III)sepulchrate electron donor system is irrelevant because the rejection is based on the combined teachings of Estabrook et al. and Creaser et al. Further, Examiner notes that the claims do not recite any such limitations on the rate of reaction.

Hence the rejection is maintained.

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak

Patent Examiner 1652

Tekchand Saidha

Primary Patent Examiner 1652